REMARKS

In the Office Action mailed March 6, 2007, the Examiner rejected Claims 16-20 and 24-28 under 35 U.S.C. §101, rejected Claims 16-20 and 24-28 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 6,130,087 (hereinafter, "the Srivastava patent"), rejected Claims 16-20 and 25-27 under 35 U.S.C. §103(a) as being obvious in light of U.S. Patent Application Publication No. 2004/0014652 (hereinafter, the "Trouet application"), and rejected Claims 16 and 18-20 under 35 U.S.C. §103(a) as being obvious in light of U.S. Patent No. 6,261,839 (hereinafter, "the Multhoff patent"). Each rejection is addressed below.

I. Rejection of Claims 16-20 and 24-28 under 35 U.S.C. §101

The Examiner alleged that the claimed methods could potentially cover naturally occurring events in the human body, and as such, rejected the claimed invention under 35 U.S.C. §101.

Claims 16, 18-20 and 24 are now cancelled, rendering the rejection of these claims moot. The Applicant reserves the right to prosecute these claims, or similar claims, at a future date.

Regarding Claims 17 and 25-28, the Applicant respectfully disagrees with the Examiner. However, in order to expedite prosecution while not acquiescing with the Examiner's arguments, the Applicant now amends 17 such that it is clearly directed to a method of treatment and does not encompass naturally occurring events such as, for example, freely circulating Granzyme B or the like. Amended Claim 17 and its dependent Claims 25-28 relate to, for example, the use of Granzyme B as a therapeutic agent for the treatment of tumor, pathogen infection and inflammatory disease, respectively, and is further characterized by the nature of the tumor cells and cells affected by the infection or disease. Support for this amendment is located throughout the Specification (see, e.g., page 10, lines 1-4 in connection with page 12, lines 3-23). Amended Claim 17 and 25-28 recites patentable subject matter.

II. Rejection of Claims 16-20 and 24-28 under 35 U.S.C. §102(b)

Claims 16-20 and 24-28 were rejected under 35 U.S.C. §102(b) as being anticipated by the Srivastava patent.

Claims 16, 18-20 and 24 are now cancelled, rendering the rejection of these claims moot. The Applicant reserves the right to prosecute these claims, or similar claims, at a future date.

Regarding Claims 17 and 25-28, the Applicant respectfully disagrees with the Examiner. However, as described above, in order to expedite prosecution while not acquiescing with the

Examiner's arguments, the Applicant now amends 17. The Srivastava patent does not teach all of the elements of Claim 17, as amended. In particular, the Srivastava patent does not teach administration of a pharmaceutically effective amount of granzyme B to a human in need thereof, as recited in the claimed invention. The Applicant requests these rejections be withdrawn.

III. Rejection of Claims 16-20 and 25-27 under 35 U.S.C. §103(a)

Claims 16-20 and 25-27 were rejected under 35 U.S.C. §103(a) as being obvious in light of the Trouet application.

Claims 16, 18-20 and 24 are now cancelled, rendering the rejection of these claims moot. The Applicant reserves the right to prosecute these claims, or similar claims, at a future date.

Regarding Claims 17 and 25-27, the Applicant respectfully disagrees with the Examiner. However, as described above, in order to expedite prosecution while not acquiescing with the Examiner's arguments, the Applicant now amends 17. As amended, the Trouet application fails to render obvious Claims 17 and 25-27.

In particular, the Examiner's statement, "[e]liminating the optional, unnecessary artificial step of coupling native Granzyme B to a protective or chaperone moiety is a prima facie obvious step of simplification by eliminating an unnecessary step" is untenable and directly opposed to the actual teaching of the Trouet application. Indeed, the Trouet application explicitly teaches that adding these moieties to the natural product Granzyme B is necessary in order to have Granzyme B traversing the cell membrane and exerting its effects intracellularly. Thus, the Trouet application states:

> "The biologically active entity may also be an entity that acts intracellularly but that is either incapable of traversing the cell membrane or does not efficiently traverse the membrane on its own...Intracellularly active agents that are not capable of traversing the cell membrane Include intracellularly active polypeptides such as granzyme B..."; see Trouet application at paragraph 0013 (emphasis added).

In paragraph 0140 the Trouet application went on to explain the killing effects of Granzyme B in that:

> "This killing effect results from the synergistic effect of perforin, a membranolytic protein and the serine protease granzyme B...Perforin allows granzyme B to reach the cytoplasm and the nucleus of cells by inducing the formation of transmembrane pores

> that constitute a passage for the enzyme...In the prodrug, the transport peptide potentially plays the role of perforin by allowing granzyme B to enter the cell and to induce apoptosis."

In view of these statements, in particular that Granzyme B is not capable of traversing the cell membrane without perforin, or in accordance with the Trouet application's invention, a transport peptide, how then can the Examiner allege that it would be obvious to spare the transport peptide moiety.

Furthermore, even if the person skilled in the art, despite the explicit teaching of the Trouet application would have tried to use the natural product Granzyme B for the treatment of, for example, tumor cells, there is no reasonable expectation of success. As demonstrated in the examples of the present application and shown in Figures 2 and 4, the apoptosis including effect of Granzyme B is dependent on the targeted cells. Thus, while Hsp70 positive colon carcinoma cells can be effectively treated, colon tumor cells which are Hsp70 membrane negative remain substantively unaffected when contacted with Granzyme B. However, prior to the present invention the dependency of Granzyme B's activity on membrane bound Hsp70 of diseased cells was not known. Thus, if the person skilled in the art would have performed experiments with Granzyme B and Hsp70 membrane negative tumor cell colonies he/she would have failed. Without knowing the reason for the failure, there would have been of course no incentive to go further, let along a hint in what direction.

In summary, the Trouet application fails to teach, suggest, enable and/or motivate the use of Granzyme B for th treatment of tumor, viral or bacterial infections or inflammatory diseases as claimed in Claim 17 and its dependent claims. The Applicant requests these rejections be withdrawn.

IV. Rejection of Claims 16 and 18-20 under 35 U.S.C. §103(a)

Claims 16 and 18-20 are now cancelled, rendering the rejection of these claims moot. The Applicant reserves the right to prosecute these claims, or similar claims, at a future date.

V. Conclusion

The Applicant believes the arguments set forth above traverse the Examiner's rejections and therefore request these alleged grounds for objection and rejection be withdrawn. Should the Examiner believe a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect.

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